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Leukocyte albumin ratio as an early predictor of mortality in critical COVID-19 patients

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Abstract
Aim: The aim of this study is to analyze the effectiveness of the leukocyte albumin ratio (LAR) in predicting mortality in critical COVID-19 patients.
Material and Methods: In this retrospectively-designed study, we evaluated a total of 98 critical patients who were hospitalized in the intensive care unit. Patients were divided into two groups according to hospital mortality as survivors (n=43) and non-survivors (n=55).
Results: The non-survivors group was statistically significantly older (67.3±9.7 versus 62.5±10.9; p=0.023). HT and DM were detected more in the non-survivors group than in the survivors group (p=0.031, p=0.018, respectively). Mean LAR values were significantly higher in non-survivors than in survivors (5.9±3.5 versus 3.3±1.4; p<0.001). LAR values was positively correlated with urea (r=0.43, p<0.001), LDH (r=0.35, p<0.001), ferritin (r=0.25, p=0.015), procalcitonin (r=0.34, p<0.001), and pro-BNP (r=0.24, p=0.015) levels. A cut-off value of 3.71 ng/mL for LAR predicted mortality with a sensitivity of 76% and a specificity of 70% (AUC:0.779 95% CI:0.689-0.870; p<0.001). Multivariable logistic regression analysis revealed that older age (OR:1.114, 95% CI:1.020-1.218; p=0.017) and increased ferritin (OR:1.003, 95% CI:1.001-1.004; p=0.002) and LAR (OR:1.583, 95% CI:1.073-2.337; p=0.021) values were independent predictors of mortality in patients with critical COVID-19.
Discussion: LAR can be a useful and prognostic marker that can be used to predict mortality in COVID-19 patients admitted to the intensive care unit.

Keywords
COVID-19, Leukocyte Albumin Ratio, Intensive Care

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Introduction

In the city of Wuhan in the People's Republic of China, an outbreak of pneumonia developed due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. SARS-CoV-2 infection causes Coronavirus disease 2019 (COVID-19) and can range in severity from asymptomatic to acute respiratory distress syndrome (ARDS), to multi-organ failure, and even death. In keeping with preliminary data from China, 81% of COVID-19 patients have mild or moderate illness, similar to colds and mild pneumonia, while 14% of patients have severe illness and 5% have life-threatening critical illnesses [2]. While the overall mortality rate of COVID-19 is estimated to be below 3%, it has been observed that the mortality rate in hospitalized patients is reported to vary between 6% and 34% [2,3-5]. Mortality rates in critical patients in intensive care units are quite high and can exceed 50% [6]. Biomarkers that can predict patients with high risk of mortality early are needed.

Leukocytes are associated with acute infections following an early inflammatory response. In previous studies, it has been demonstrated that increased leukocyte count is related to severe disease and mortality in COVID-19 patients [7]. Albumin is a negative acute-phase protein and systemic inflammatory response is independently associated with circulating albumin concentrations [8]. The mechanisms behind hypoalbuminemia in COVID-19 patients have not yet been fully understood, but one possible mechanism is a cytokine storm associated with severe disease. Hypoalbuminemia in cases of COVID-19 is thought to be due to increased capillary permeability, resulting in albumin escaping into the interstitial space, rather than a decrease in albumin synthesis [9-11]. It has been demonstrated in some studies that low albumin levels are predictors of severe disease and mortality in COVID-19 patients [11-13].

The aim of this single-center, retrospective study was to analyze the effectiveness of the leukocyte/albumin ratio (LAR) as a predictor of mortality in COVID-19 patients hospitalized in intensive care.

Material and Methods

Study Population

Ninety-eight patients with COVID-19 infections who were hospitalized in the Intensive Care Unit of Malatya Turgut Ozal University Training and Research Hospital between September 2020 and October 2020 were retrospectively included in the study. Patients included in our study were older than 18 years old and no gender difference was observed between patients.

COVID-19 diagnosis was defined as a SARS-CoV-2 positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) from a nasal and/or throat swab together with signs, symptoms, or radiological findings suggestive of COVID-19 infection.

Data collection

Patient characteristics, clinical features and laboratory data were collected from a digital archive system in our hospital. Routine hematological and biochemical tests included leukocyte count, C-reactive protein (CRP), procalcitonin, d-dimer, fibrinogen, cardiac biomarkers, and liver/kidney function tests. The LAR was measured by dividing the leukocyte count by the albumin value. The laboratory data of patients within the first 8 hours after admission to the intensive care unit were evaluated.

Laboratory Analyzes

Complete blood cell counts were analyzed via a high-volume hematology analyzer (SYSMEX, Automated Hematology, Wakinohama-Kaigondori, Chu-ku Kobe JAPAN). The blood samples were collected in potassium-ethylenediaminetetraacetic acid tubes and analyzed within one hour after venipuncture. The albumin levels were determined via a nephelometric analyzer (ARCHITECT, Toshiba, Abbott Park, USA) by the immunonephelometry method.

Ethics

The study was conducted in accordance with the Helsinki Declaration and was approved by the Ethical Committee of the Medicine Faculty of Firat University (issue:2021/02-31)

Statistical Analyses

IBM SPSS Statistics 25 software was used for statistical analysis, results were stated as mean ± SD. The level of statistical significance was regarded as $p<0.05$. To compare two independent samples, the student's t-test was conducted. To compare multiple samples, the One-Way ANOVA test was used. Parametric variables were evaluated using Pearson's correlation analysis. In the study, multivariate analyses were conducted using binary logistic regression to evaluate variables that could predict mortality. In the analysis, a 95% confidence interval (CI) was adopted while calculating the odds ratios (ORs). The "Receiver Operating Characteristic" (ROC) analysis method was used to determine the cut-off value for inflammatory markers. Additionally, the ROC value was used for determining the sensitivity and specificity values for inflammatory markers. The "Area under Curve" (AUC) value was determined with the ROC curve.

Results

Baseline characteristics of patients

In this study a total of 98 patients were included, 76 of them were men and 22 were women. While 55 (56.1%) of the patients died during the intensive care follow-up, 43 (43.9%) patients were discharged. The mean age of the patients was 65.1±10.4 years. There was no difference between the two groups in terms of gender ($p=0.252$, x2:1.31). Non-survivors were found to be statistically significantly older than surviving patients (67.3 ± 9.7 versus 62.5±10.9; $p=0.023$). While HT and DM were found statistically much more frequent in the non-survivors group ($p=0.031$, $p=0.018$, respectively), no significant difference was observed on the basis of other comorbidities. When patients first admitted to intensive care, 38 (38.8%) patients had invasive mechanical ventilation, 33 (33.7%) patients had noninvasive mechanical ventilation (NIMV), 27 (27.6%) patients had high flow oxygen (HFO). In the non-survivors group, invasive mechanical ventilation application was found to be significantly higher ($p<0.001$). On the other hand, in the survivors group, HFO application was found to be significantly higher ($p<0.001$) (Table 1). All patients had bilateral pneumonia findings consistent with COVID-19, confirmed by thoracic CT.

Comparison of laboratory tests between survivors and non-survivors

Analysis of complete blood count parameters demonstrated that the non-survivors group had a significantly higher

Table 1. Comparison of baseline characteristics and laboratory tests between survivors and non-survivors

	Non-survivors (n=55)	Survivors (n=43)	p-value
Age, years	67.2 ±9.6	62.4 ±10.9	0.023
Sex, male, n(%)	45 (%59.2)	31 (%40.8)	0.252
Comorbidities			
Hypertension	49 (%61.3)	31 (%38.8)	0.031
Diabetes Mellitius	27 (%71.1)	11 (%28.9)	0.018
Cardiovasculer Disease	26 (%60.5)	17 (%39.5)	0.444
Chronic Lung Disease	12 (%46.2)	14 (%53.8)	0.232
Chronic Kidney Disease	8 (%80)	2 (%20)	0.108
Cerebrovascular Disease	3 (%75)	1 (%25)	0.437
Respiratory Support			
Invasive Mechanical ventilation	30 (%78.9)	8 (%21.1)	<0.001
Noninvasive Mechanical Ventilation	21 (%63.6)	12 (%36.4)	0.285
High Flow Oxygen Therapy	4 (%14.8)	23 (%85.2)	<0.001
Hematological markers			
Leucocyte, 10^3/L	14.3 ±6.5	9.5 ±4.0	<0.001
Neutrophil, 10^3/L	12.6 ±6.5	8.0 ±3.7	<0.001
Lymphocyte, 10^3/L	0,7 ±0.4	0,9 ±0.9	0.078
Hemoglobin, g/dL	12.6 ±2.1	12.7 ±1.7	0.777
Hematocrit, %	38.9 ±6.0	38.2 ±6.4	0.590
Platelet, 10^3/L	272.3±117.5	248.6 ±106.9	0.306
Biochemical markers			
Albumin, g/dL	2.5 ±0.5	2.9 ±0.3	<0.001
Urea, mg/dL	95.5 ±65.2	52.1 ±24.4	<0.001
Creatinine mg/dL	1.5 ±1.3	0.9 ±0.4	0.004
Serum sodium, mmol/L	141.4 ±6.2	136.2 ±3.9	<0.001
Serum potassium mmol/L	4.4 ±0.7	4.3 ±0.7	0.630
Serum calcium, mmol/L	7.9 ±0.6	8.2 ±0.5	0.025
LDH, IU/L	682.5±251.4	420.9 ±226.6	<0.001
Cardiac markers			
CK, mcg	226.5±249.8	84 ±63.2	<0.001
D-dimer, µg FEU/mL	13.6 ±8.3	7.5 ±5.7	0.035
Pro-BNP, pg/mL	2403 ±2640	1366 ±20 48	0.036
Inflammatory markers			
Ferritin, ng/mL	1131 ±650.1	550 ±459.6	<0.001
Fibrinogen, mg/dL	599.0±208.5	452.7 ±226.1	0.001
CRP, mg/dL	13.6 ±8.3	7.5 ±5.7	<0.001
Procalcitonin, ng/mL	2.1 ±3.4	0.2 ±0.2	<0.001
Leucocyte Albumin Ratio	5.9±3.5	3.3±1.4	<0.001

Table 2. ROC analysis results of inflammatory markers to predict mortality in COVID-19 patients (CRP: C-reactive protein, LAR: Leukocyte- to- albumin ratio)

	AUC (95%CI)	Cut-off	Sensitivity (%)	Specificity (%)	p
Leukocyte	0.734	10.75	70	63	<0.001
CRP	0.724	8.9	66	60	<0.001
Procalcitonin	0.761	0.2	71	67	<0.001
Fibrinogen	0.683	487	69	65	0.002
Ferritin	0.764	559	73	70	<0.001
Albumin	0.273	2.85	67	65	<0.001
Leukocyte/ albumin ratio	0.779	3.71	76	70	<0.001

Table 3. Results of binary logistic regression analysis of the potential predictors of mortality in COVID-19 patients

Independent variables	OR value	95% CI	p-value
Age, yrs	1.114	(1.020-1.218)	0.017
Sex, male	0.743	(0.156-3.547)	0.71
Urea, mg/dL	1.004	(0.982-1.028)	0.70
LDH, mg/dL	1.002	(0.998-1.005)	0.31
CK, mcg	1.006	(0.998-1.014)	0.12
Ferritin, mg/dL	1.003	(1.001-1.004)	0.002
Fibrinogen, mg/dL	1.003	(0.999-1.006)	0.10
CRP, mg/L	1.066	(0.943-1.204)	0.31
Procalcitonin, ng/mL	1.570	(0.704-3.501)	0.27
Leukocyte/albumin ratio	1.583	(1.073-2.337)	0.021

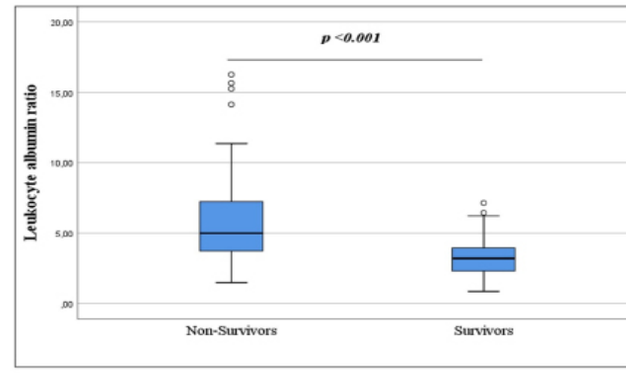

Figure 1. Mean LAR values in non-survivors and survivors

leukocyte count than the survivors group (p<0.001). Analysis of basic biochemical markers showed that urea, creatinine, sodium and LDH levels were significantly higher (p<0.001, p=0.004, p<0.001, and p<0.001, respectively), and albumin and calcium levels was significantly lower in the non-surviving patients (p<0.001, p=0.025). Analysis of inflammatory markers of the patients revealed that the non-survivors group had higher CRP, fibrinogen, ferritin and procalcitonin levels in significant numbers in the comparison with the patients of the survivors group (for all; p<0.001). In the analysis of cardiac biomarkers, CK, d-dimer and pro-BNP levels were found to be significantly higher in non-surviving patients from a statistical standpoint (p<0.001, p=0.035 and p=0.036; respectively). Additionally, the mean LAR values were significantly higher in the non-surviving patients compared to the survivors (5.9±3.5 versus 3.3±1.4; p<0.001) (Table 1, Figure 1).

Correlation Analysis

Pearson's correlation analysis was used to explore the relationship between LAR and biochemical markers. LAR values was positively correlated with urea (r=0.43, p<0.001), LDH (r=0.35, p<0.001), ferritin (r=0.25 p=0.015), procalcitonin (r=0.34, p<0.001), and pro-BNP (r=0.24 p=0.015) levels. Linear correlation analysis graphs are given in Figures 2 and Figure 3.

ROC Curve Analysis

The efficacy of inflammatory markers for the prediction of mortality was evaluated using ROC analysis. Areas under the curve (AUC) of leukocyte, CRP, procalcitonin, fibrinogen, ferritin, albumin and LAR were found as 0.734 (p<0.001), 0.724 (p<0.001), 0.761 (p<0.001), 0.683 (p=0.002), 0.764 (p<0.001),

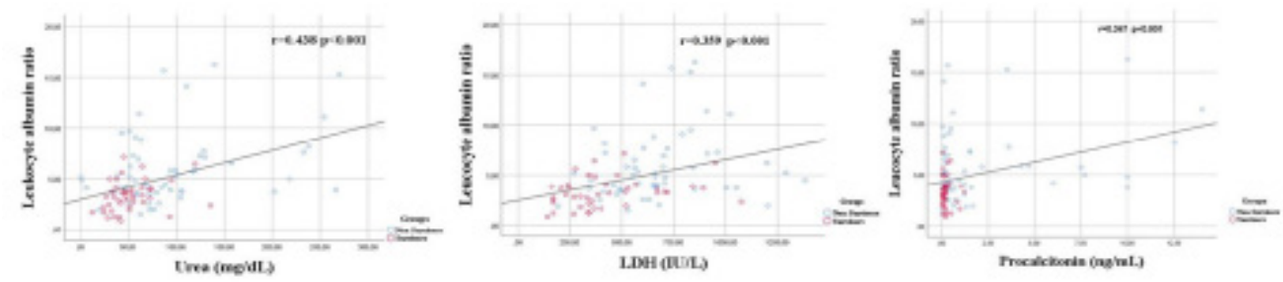

Figure 2. Correlation graphs between LAR and LDH, urea, and procalcitonin

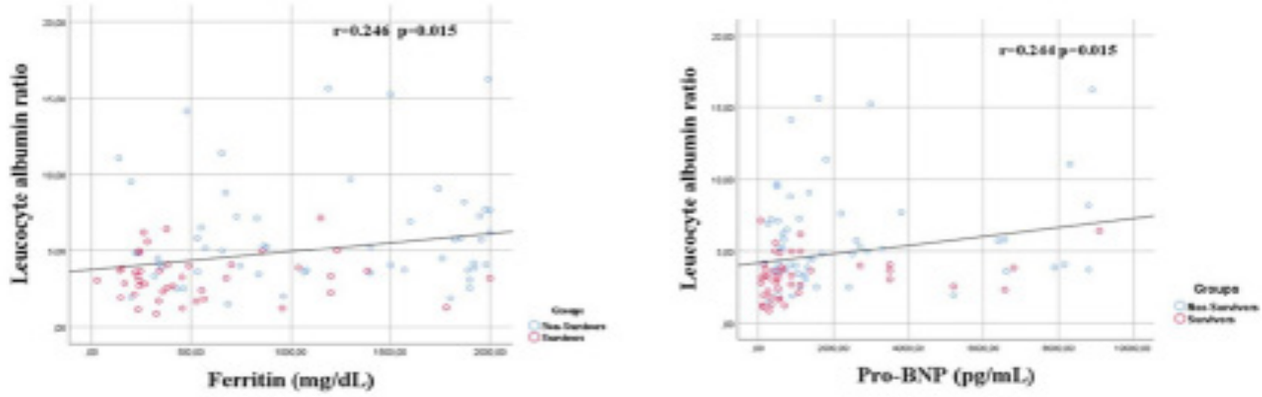

Figure 3. Correlation graphs between LAR and ferritin, pro-BNP

0.273 (p<0.001) and 0.779 (p<0.001), respectively. Among these parameters, LAR occupied the maximum area with 0.779 (AUC:0.779 95% CI:0.689-0.870, p<0.001). When the cut-off value for LAR in predicting mortality was determined to be 3.71, the sensitivity was determined as 76%, while the specificity was 70% (Table 2).

Logistic Regression Analysis

Multivariable logistic regression analysis, which included age, sex, urea, LDH, CK, ferritin, fibrinogen, CRP, procalcitonin, LAR revealed that older age (OR: 1.114, 95% CI: 1.020-1.218; p=0.017) and increased ferritin (OR: 1.003, 95% CI: 1.001-1.004; p=0.002) and LAR (OR: 1.583, 95% CI: 1.073-2.337; p=0.021) values were independent predictors of mortality in patients with critical COVID-19 during hospitalization (Table 3).

Discussion

The results of the present study indicate that LAR values were significantly higher in the non-surviving patients compared to the surviving patients. Multivariable logistic regression analysis revealed that increased LAR values were predictors of mortality in patients with critical a COVID-19 infection during hospitalization. Additionally, LAR was found to have a reasonable sensitivity (76%) and specificity (70%) in predicting non-survival patients.

The mortality rate in critical COVID-19 patients hospitalized in intensive care is quite high, and in a cohort study, hospital mortality was found to be at 53.4% [7]. In accordance with the literature data, mortality was found to be 56.1% in our study. In our study, there was a high rate of mechanical ventilation during intensive care admission, and this may explain the high mortality rate. Additionally, in our study it was determined that advanced age is an independent risk factor for mortality, and DM and HT are more common in non-surviving patients.

In many previous studies, it has been observed that biomarkers such as CRP, D-dimer, ferritin, cardiac troponin, IL-6, leukocyte and lymphocyte count can be used in risk stratification to predict disease severity [15]. Similarly, elevated leukocyte levels have been found to be associated with severe disease and mortality [7,16]. On par with the literature, in our study leukocyte levels were found to be elevated in non-survivor patients compared to those who survived. Additionally, when the cut-off value for leukocyte count was taken as 10.75 in ROC analysis, it was observed that it predicted mortality with 70% sensitivity and 63% specificity.

Albumin is known as a negative acute phase reactant, and circulating albumin concentrations are inversely proportional to the magnitude of the systemic inflammatory response. In cases of acute inflammation, while the production and secretion of pro-coagulants such as C-reactive protein and fibrinogen rise, plasma concentrations of constitutive proteins such as albumin and transferrin fall [8,17]. Various studies have shown that low albumin levels are predictors of severe disease and mortality in COVID-19 patients [11-13]. Similar to the literature, in our study we found the level of albumin to be higher in non-survivor patients compared to those who survived. Additionally, when the cut-off value for albumin was taken as 2.85, it was found that it showed 67% sensitivity and 65% specificity in predicting mortality.

Upon examination of the literature, it was seen that there was no study analyzing the importance of LAR in predicting mortality in COVID-19 patients. Wang et al. showed in their study that the CRP-albumin ratio is an independent risk factor for predicting

mortality at an early stage of COVID-19 infection [18]. It has been reported that the ratio of fibrinogen-albumin in COVID-19 patients is an independent risk factor for severe disease and that the increased fibrinogen albumin ratio may be related to cytokine storms [19]. In another study, it was observed that the ratio of neutrophil-albumin was higher in critically ill patients compared to noncritical patients, and this situation was found to be associated with a poor prognosis [20].

According to the results of our study, LAR had a stronger predictive value for predicting mortality than leukocyte alone or albumin alone, as well as other analyzed inflammatory markers (CRP, procalcitonin, fibrinogen, and ferritin). LAR was found to be an independent predictor of mortality and showed an important performance for predicting hospital mortality. In addition, it was found that LAR levels were positively correlated with urea, LDH, ferritin, procalcitonin and pro BNP levels. High LAR indicates an imbalance in inflammatory response, and may be a marker showing disease severity in conditions such as sepsis [21].

Some limitations should be interpreted with our study. Our study is a single center, retrospective, and partially includes a small number of patients. The death rate from COVID-19-related or other specific causes alone is unknown. Finally, only LAR levels at the beginning of admission to intensive care were analyzed in our study.

As a result, it was found that the LAR index is an important marker in predicting hospital mortality, and is also an independent predictor of hospital mortality. More research is needed to validate our findings, evaluate the predictive ability of baseline LAR values, and analyze changes in LAR values during follow-up/treatment.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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